

U.S. Patent Application No. 10/075,404
Response to the Office Action Mailed October 11, 2005
Request for Reconsideration dated February 13, 2006

REMARKS/ARGUMENTS

Continued examination and favorable consideration of the present application are respectfully requested.

Claims 23-40 remain pending in this application. Claim 23 has been amended. Support for the amendment to claim 23 is found at least in previously presented claim 24. No new matter has been added.

Miscellaneous

Applicants wish to thank Examiner Noguerola for the courtesy of the telephone conference with J. Singh on November 29, 2005.

Double Patenting

Claims 23 and 25-32 are rejected in two separate rejections at pages 5 and 7 of the Office Action, under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 1 of U.S. Patent No. 6,372,106 B1 to Johnson *et al.* in view of Knox *et al.* ("Volume Expansion and Loss of Sample due to Initial Self-heating in Capillary Electroseparation (CES) Systems," *Chromatographia*, Vol. 38, No. 5/6, March 1994) and McCormick ("Capillary Zone Electrophoretic Separation of Peptides and Proteins Using Low pH Buffers in Modified Silica Capillaries," *Anal. Chem.*, 1988, 60, 2322-2328). Reconsideration and withdrawal of the rejections are respectfully requested.

Claim 23 has been amended. Each of claims 25-32 depends directly or indirectly on claim 23. Applicants respectfully traverse both rejections and request that, if not withdrawn, at a

U.S. Patent Application No. 10/075,404
Response to the Office Action Mailed October 11, 2005
Request for Reconsideration dated February 13, 2006

minimum the rejections be held in abeyance until the claims in the application are otherwise in condition for allowance.

Rejection of Claims

At page 9 of the Office Action, the Examiner rejected claims 23, 24, 27-32, and 35-40 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Liu *et al.* ("Separation of Double- and Single-stranded DNA Restriction Fragments: Capillary Electrophoresis with Polymer Solutions under Alkaline Conditions," *Anal. Chem.*, 1999, 71, 1668-1673) (hereinafter "Liu *et al.*") in view of Knox *et al.* ("Volume Expansion and Loss of Sample due to Initial Self-heating in Capillary Electroseparation (CES) Systems," *Chromatographia*, Vol. 38, No. 5/6, March 1994) (hereinafter "Knox *et al.*"), and McCormick ("Capillary Zone Electrophoretic Separation of Peptides and Proteins Using Low pH Buffers in Modified Silica Capillaries," *Anal. Chem.*, 1988, 60, 2322-2328) (hereinafter "McCormick"). Applicants respectfully traverse this rejection. Applicants incorporate by reference herein, reiterate, and expand upon, the Reply filed August 2, 2005.

On page 2 of the Office Action the Examiner indicates that "Applicant's arguments filed August 2, 2005 have been fully considered but they are not deemed persuasive." Applicants respectfully disagree, because their arguments should be considered persuasive.

On the same page of the Office Action, in responding to Applicants' previous Reply, the Examiner first states that "Liu *et al.* is the base reference for the rejections." The Examiner is not aware of any requirement under 35 U.S.C. §103(a) that the base reference must provide motivation for using the teaching of a secondary reference." Applicants agree with the Examiner, however, no such argument was made. Rather, Applicants were establishing that *none* of the

U.S. Patent Application No. 10/075,404
Response to the Office Action Mailed October 11, 2005
Request for Reconsideration dated February 13, 2006

cited references contained any suggestion or motivation, whatsoever, that would permit them to be properly combined to make the rejection under 35 U.S.C. §103(a). In doing so, Applicants specifically pointed to reasons why Liu et al., as one of three cited references, failed to meet this requirement. Applicants also indicated that *neither* of the secondary references contained motivation to be combined. Applicants reiterate that neither a suggestion nor a motivation to combine the art is present in any of the cited references. Thus, there is no basis for making the § 103 rejection.

At page 2 of the Office Action, the Examiner next refers to Applicants' argument made in the Reply filed August 2, 2005, noting that Applicants asserted that: "At page 1668, first full paragraph, Liu et al. refers to another publication that specifically notes "the other fragments of 23 kbp were *successfully separated* using this ultra-diluted HEC solution under *constant field strength*." (Emphasis in original.)

The Examiner indicated that he could not locate the quoted clause. Applicants regret any confusion or inconvenience resulting from this error. The reply should have referred to the second full paragraph and not the first full paragraph of page 1668 (after the abstract) and the quotation marks should have been before "23," not "the other fragments."

Applicants request that the Examiner reconsider the recitation in Liu et al. that "DNA fragments up to 23kbp were *successfully separated* using this ultra-diluted HEC solution under *constant field strength*" (Liu et al. at page 1668, second column, first full paragraph, last sentence) (Emphasis added).

At page 2 of the Office Action, the Examiner next argues that "In any event as acknowledged by Applicants this quotation is from another publication. So its relevance to

U.S. Patent Application No. 10/075,404
Response to the Office Action Mailed October 11, 2005
Request for Reconsideration dated February 13, 2006

limiting how Liu et al. performs capillary electrophoresis is not apparent." Applicants respectfully disagree that the statement is not relevant.

The Examiner must consider the cited reference as a whole and cannot ignore information in the reference that contradicts the Examiner's argument forming a basis for the rejection. Liu et al. fails to disclose or even suggest using a slow controlled voltage ramp rate. Furthermore, Liu et al. refers to exactly the opposite, i.e. that there has been successful separation by others using constant field strength. Therefore, the reference, *as a whole*, not only fails to suggest using a slow controlled ramp rate, but actually provides evidence against using such an approach.

On page 3, the Examiner also argues that "as a general principle it was known in the art at the time of the invention that a high ramp rate would adversely affect the separation of a capillary electrophoresis system. The stated general principle is the motivation." Applicants disagree for several reasons.

First, the Examiner has failed to establish that there actually is such a general principle. It appears that the Examiner is attempting to take judicial notice of the facts. This is improper without appropriate support. The MPEP clearly states at §2144.03(A) (MPEP Rev. 3, August 2005, 2100-142, right hand column, last paragraph):

It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestioning demonstration as being well-known.

(Emphasis in original).

The facts set forth by the Examiner are not capable of instant and unquestioning demonstration as being well-known and the Examiner has failed to cite a prior art reference to

U.S. Patent Application No. 10/075,404
Response to the Office Action Mailed October 11, 2005
Request for Reconsideration dated February 13, 2006

support the contention that a high ramp rate would adversely affect separation in a capillary electrophoresis apparatus. Thus, the rejection cannot be sustained.

If the Examiner maintains the rejection, Applicants respectfully request the Examiner to cite a reference indicating such a general principle. Even assuming that a specific result is obtained in a single publication, this does not establish a general principle. If a reference establishing the general principle set forth by the Examiner is not cited, it is assumed that the Examiner is basing the conclusion on the Examiner's personal knowledge. Therefore, if a reference is not cited, and Applicants respectfully request an Examiner's Affidavit as required by MPEP §2144.03(C).

If the examiner is relying on personal knowledge to support the finding of what is known in the art, the examiner *must* provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. See 37 CFR 1.104(d)2.

(MPEP Rev. 3, August 2005, 2100-144, left-hand column, first paragraph). (Emphasis added).

Such a request by Applicants must be responded to as required under 37 CFR §1.104(d)2, should the rejection be maintained.

Second, on page 3 of the Office Action, the Examiner also argues that in Liu et al. "[T]he run voltage is either achieved very quickly ... or at a slow ramp rate," and that "the fairest assumption is that Liu et al. achieves the 6,000 volts very quickly, that is, at a very high ramp rate." In view of the fact that Liu et al. discusses the *successful* use of a constant field strength and no ramp rate whatsoever is discussed in Liu et al., Applicants fail to understand how the Examiner can assume that any ramp rate, whatsoever, is used in Liu et al.

As evidenced above, Liu et al. points to how *successful* constant field strength can be for a desired separation. Therefore, Liu et al. cannot be fairly combined with the teachings of Knox

U.S. Patent Application No. 10/075,404
Response to the Office Action Mailed October 11, 2005
Request for Reconsideration dated February 13, 2006

et al. or McCormick to arrive at the claimed invention. If Liu et al. notes how successful a constant field strength can be, why would Liu et al. be motivated to use a slow ramp rate?

The Examiner also refers in a footnote at page 3 of the Office Action, to a manual that may or may not have been used by Liu et al. No evidence, however, is presented that Liu et al. actually used such a manual or was even aware of its contents. In any event, even if Liu et al. used such a manual, the Examiner states that the system "is configured for *optional* voltage ramping." The fact that the system may be configured for *optional* voltage ramping indicates that other alternatives, e.g. constant field strength or step increases in the voltage, may also be used. Therefore, where is the motivation to use a *slow* ramp rate?

Even, assuming *arguendo*, that the Examiner's assumption is correct about a high ramp rate, this is exactly the opposite of what is described in the pending claims and contradicts the Examiner's assertions about a motivation to use *slow* ramp rate. Therefore, Liu et al. fails to teach establishing the run field at a ramp rate no greater than about 5 V/cm-s, as presently claimed in independent claims 23 and 24. Thus, Liu et al. *and* the additional cited art clearly lacks at least one aspect of the present invention.

The Examiner also refers to McCormick with reference to claims 23 and 25 and reduction of peak broadening, but acknowledges that McCormick does not describe nucleic acids. Claim 23 has been amended to refer to nucleic acids. Therefore, all claims now refer to nucleic acids and McCormick cannot support a rejection based on the combination of references. McCormick provides no results, whatsoever, showing nucleic acid separations. Merely because a certain result may be obtained when electrophoretically separating proteins, there is no *a priori* reason to assume that similar results would necessarily be obtained with nucleic acids. If the rejection is maintained, the Examiner is respectfully requested to provide a reference showing that

U.S. Patent Application No. 10/075,404
Response to the Office Action Mailed October 11, 2005
Request for Reconsideration dated February 13, 2006

electrophoretic parameters used to separate proteins will necessarily work with nucleic acids. In particular, Applicants request information in this regard to the conditions for establishing an appropriate ramp rate during electrophoresis of nucleic acids.

At a minimum, the previous rejection of claim 24 cannot stand. Claim 24 refers to a slow ramp rate used to separate nucleic acids that resulted in reduced peak broadening. The Examiner rejected claim 24 using the following combination:

- 1) A reference that pointed to successful results using constant field strength to separate nucleic acids (Liu et al.) – *however, no mention is made about voltage ramp rate,*
- 2) A reference that discussed ramp rates as they affected self-heating and liquid expansion (Knox et al.) – *however, the reference fails to discuss nucleic acids or peak broadening,* and
- 3) A reference describing the electrophoretic separation of proteins (McCormick) – *however, the reference fails to describe separating nucleic acids.*

The combination of three such references cannot render obvious the pending claims.

In addition to addressing Applicants previous arguments, the Examiner provides additional elaboration at page 10 of the Office Action. The Examiner states that “Although McCormick does not mention using a non-crosslinked polymer or nucleic acid it should be noted that McCormick does disclose coating the inside of the capillary with polymer and separating proteins.” It is respectfully submitted that this is irrelevant to the claims being rejected.

Regardless of whether McCormick may coat the inside of the capillary with polymer, “coating the inside of the capillary” is not the same as using a “fluid separation medium” containing a “*non-crosslinked*” polymer. Even if, assuming *arguendo*, “coating” is considered the same as “fluid separation medium,” the Examiner fails to point to any indication that the

U.S. Patent Application No. 10/075,404
Response to the Office Action Mailed October 11, 2005
Request for Reconsideration dated February 13, 2006

polymer is non-crosslinked. Therefore, McCormick clearly fails to teach or suggest at least the use of a non-crosslinked fluid separation medium as set forth in claim 23, and fails to provide any motivation to combine its teachings with the additionally cited art.

At page 10 of the Office Action, last paragraph, the Examiner argues that "barring a contrary showing, all of these claims only provide for optimized ranges or values." Applicants disagree.

The Examiner has failed to provide a showing from the combination of the art that it would be obvious to: 1) improve peak broadening during electrophoresis of a nucleic acid, *not a protein*; 2) use any ramp rate whatsoever; and 3) use a non-crosslinked polymer as a fluid separation medium. Before the Examiner can argue that Applicants are merely optimizing conditions, the Examiner must show at least the above. This has not been done. Even if this could be shown, the Examiner should also show the above aspects of a claim using a different ramp rate that is presumably close to what the Applicants have used in their claimed method, that would produce reduced peak broadening during an electrophoresis run. None of this has been done. Thus, given the art cited by the Examiner, Applicants' invention using a ramp rate other than that claimed has not been shown. If Applicants' invention, minus merely the ramp rate is not shown by the Examiner, there can be no mere optimization of values or ranges that can be conducted to arrive at Applicants' invention. The rejection is overcome and should be withdrawn.

In the recent Federal Circuit decision *In re Scott E. Johnston*, 05-1321, *Page 5 (Fed. Cir., Jan. 30, 2006) (Fed. Cir. BBS), the court reiterated the following:

Precedent requires that to find a combination obvious there must be some teaching, suggestion, or motivation in the prior art to select the teachings of separate references and combine them to

U.S. Patent Application No. 10/075,404
Response to the Office Action Mailed October 11, 2005
Request for Reconsideration dated February 13, 2006

produce the claimed combination. Karsten Mfg. Corp. v. Cleveland Golf Co., 242 F.3d 1376, 1385 (Fed. Cir. 2001) ("In holding an invention obvious in view of a combination of references, there must be some suggestion, motivation, or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in the way that would produce the claimed invention.") . . . Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself.") . . . See, In re Rouffet, 149 F.3d 1350, 1358 (Fed. Cir. 1998) (obviousness requires proof "that the skilled artisan...would select the elements from the cited prior art references for combination in the manner claimed.")

The Examiner has failed to apply the above legal standards because:

1. No motivation has been provided from the prior art to support the selection of teachings from separate references for combination.
2. No motivation or suggestion has been provided from the prior art to combine the teachings in the way that would produce the claimed invention.
3. No reason other than hindsight gleaned from Applicants' specification has been provided for the combination.
4. No proof has been provided that a skilled artisan would select the elements from the cited art for combination in the manner claimed.

Based on all of the above, neither the motivation to combine the cited art nor a reasonable expectation of obtaining the invention of claims 23, 24, 27-32 and 35-40 exists. Therefore, this rejection is overcome and should be withdrawn. All pending claims should be allowed.

In the Office Action at page 11, the Examiner rejected claims 25, 36, 33, and 34 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Liu et al., in view of

U.S. Patent Application No. 10/075,404
Response to the Office Action Mailed October 11, 2005
Request for Reconsideration dated February 13, 2006

Knox, et al., and McCormick as applied previously to claims 23 and 24 above, and further in view of the CAPLUS abstract of Isaaq, et al. under Alkaline Conditions," Anal. Chem. 1999, 71, 1668-1673) ("The Effect of Column Length, Applied Voltage, Gel Type, and Concentration on the Capillary Electrophoresis Separation of DNA Fragments and Polymerase Chain Reaction Products," *Electrophoresis* (1997), 18(7), 1153-1158), hereinafter "Isaaq." Applicants respectfully traverse this rejection.

For all the reasons stated above in addressing the Examiner's earlier comments, the combination of Liu et al., Knox et al., and McCormick fails to teach or suggest establishing the run field at a ramp rate no greater than about 5 V/cm-s as claimed in claims 25, 26, 33, and 34. The additionally cited art of Isaaq fails to remedy the deficits in the combination of Liu et al., Knox et al., and McCormick.

Based on this, neither the motivation to combine the cited art nor a reasonable expectation of successfully obtaining the claimed invention would exist based on the cited four-way combination of art. Therefore, this rejection is overcome and should be withdrawn, and the pending claims should be allowed.

European Search Report

In the Office Action at pages 12 and 13, the Examiner refers to several pieces of art that were cited in a European Search Report. The Examiner failed to formally cite any of these documents in a rejection against the pending claims. Therefore, Applicants need not specifically address the cited documents, however, but note for the record that they may not necessarily agree with comments about the references made by the Examiner. Furthermore, Applicants reserve the

U.S. Patent Application No. 10/075,404
Response to the Office Action Mailed October 11, 2005
Request for Reconsideration dated February 13, 2006

right to rebut any of the cited documents, should the Examiner include them at a later date in a rejection against any of the claims.

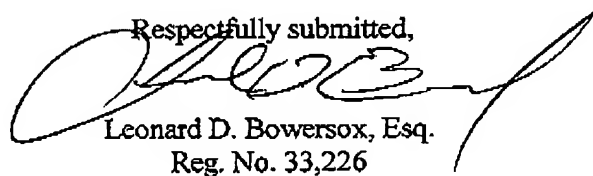
CONCLUSION

In view of the foregoing Amendment and Remarks, Applicants respectfully request favorable reconsideration of the present application and a timely allowance of the pending claims.

Should the Examiner deem that any further action by Applicants or Applicants' undersigned representative is desirable and/or necessary, the Examiner is invited to telephone the undersigned at the number set forth below.

If there are any fee(s) due in connection with the filing of this response, please charge the fee(s) to Deposit Account No. 50-0925. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such extension is requested and should also be charged to said Deposit Account.

Respectfully submitted,



Leonard D. Bowersox, Esq.
Reg. No. 33,226

KILYK & BOWERSOX, P.L.L.C.
3603-E Chain Bridge Road
Fairfax, Virginia 22030
Tel.: (703) 385-9688
Fac.: (703) 385-9719